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INTERNAL MEDICINE

IgG4-related pleural disease diagnosed by a re-evaluation of chronic bilateral pleuritis in a patient who experienced occasional acute left bacterial pleuritis

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~~Acute left bacterial pleuritis in a patient with chronic bilateral IgG4-related pleuritis~~

IgG4-related pleural disease diagnosed by a re-evaluation of chronic bilateral pleuritis in a patient who experienced occasional acute left bacterial pleuritis

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ABSTRACT

A 78-year-old male with cryptogenic chronic bilateral lymphoplasmacytic pleuritis, diagnosed based on left parietal pleural biopsy specimens obtained by pleuroscopy, developed acute left bacterial pleuritis. The left pleural effusion was neutrophil dominant, however, the right pleural effusion showed lymphoplasmacytic infiltration. Examinations found that his serum IgG4 concentration was increased, with a higher level of IgG4 in the right pleural effusion. Re-evaluation of the previous biopsy specimens using an immunostaining method revealed numerous IgG4-positive plasma cell infiltrations with IgG4-positive/IgG-positive plasma cells at 85.4%. Accordingly, the new diagnosis of the patient was considered to be chronic bilateral IgG4-related pleuritis. (97words)

Key words: pleuritis, lymphoplasmacytic, IgG4, pleuroscopy

INTRODUCTION

Immunoglobulin (Ig) G4-related lung and plural disease has been receiving increasing attention [1]. Recently, Shrestha *et al.* reported 6 patients who were diagnosed with lung involvement in IgG4-related autoimmune pancreatitis (AIP) [2]. Interestingly, all 6 patients had fibrinous pleuritis confirmed histopathologically, and one of them showed a right pleural effusion radiologically [2]. However, the clinical features of IgG4-related lung and pleural diseases are not fully understood. We herein report a patient who had been diagnosed with chronic bilateral lymphoplasmacytic pleuritis who developed acute left bacterial pleuritis, which was identified to be IgG4-related pleural disease.

CASE REPORT

A 78-year-old male was admitted to our hospital (Shinshu University School of Medicine, Matsumoto, Japan) complaining of general fatigue and fever without pain and dyspnea in July 2008. He had no family history of pancreatic disease, collagen disease, or autoimmune disease. He had a history of gall bladder stones and underwent a cholecystectomy at 68 years of age.

At 74 years of age, he developed a bilateral painless pleural effusion without

associated fever. His bilateral pleural effusions were both exudative and mononuclear cell dominant. Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed no abnormal uptake. In 2004, a pleuroscopic parietal pleural biopsy in the left thorax was performed and lymphoplasmacytic pleuritis of unknown etiology was diagnosed. Bacterial culture and polymerase chain reaction (PCR) analysis of the pleural effusion for *Mycobacterium tuberculosis, avium,* and *intracellulare* DNA were all negative. Adenosine deaminase (ADA) concentrations in the pleural effusion were measured three times from both sides in 2004. Because the values of ADA in the pleural effusion were 34.1, 36.5, and 46.7 (U/L), we could not conclusively rule out the possibility that the patient might be affected by tuberculous pleuritis [3]. Although he was received oral antituberculosis agents for 6 months in 2005, the bilateral pleural effusion did not decrease at all. We therefore believed that his chronic bilateral pleuritis was not tuberculous pleuritis. He was placed under clinical observation with diuretics, but the bilateral pleural effusion still did not show any remarkable change until the time of his present administration.

Laboratory examinations showed the following values (normal range): peripheral white blood cell count, 13,110 /μL; C-reactive protein, 25.3 mg/dL; total protein (TP), 7.4 g/dL; albumin, 3.3 g/dL; lactate dehydrogenase (LD), 175 IU/L (<220); and IgG,

1604 mg/dL (<1700). The serum concentrations of the IgG subclasses were as follows: IgG1, 791 mg/dL (<1080); IgG2, 777 mg/dL (<931); IgG3, 84 mg/dL (<121); and IgG4, 483 mg/dL (<108), and IgG4/IgG 30.1%. The serum autoantibodies were all negative, including antinuclear antibody (ANA), rheumatoid factor (RF), anti-double-stranded DNA antibody, anti-RNP antibody, anti-Sjögren's syndrome (SS)-A antibody, SS-B antibody, and anti-neutrophil cytoplasmic autoantibody (ANCA). The serum level of the soluble interleukin-2 receptor was 907 U/mL (<421) and angiotensin converting enzyme (ACE) was 12.9 U/L (<25). His electrophoretogram of a blood sample did not show any abnormal bands. His thyroid function was normal and the level of brain natriuretic peptide (BNP) in the blood was normal. Proteinuria was not observed.

A chest X-ray showed bilateral pleural effusion as had been noted prior to the present admission without infiltration in the lung fields (Fig. 1). We took a cytology of the right pleural effusion percutaneously and examined the fluid on the day of admission. However, seven days after admission, his chest X-ray revealed a rapid increase of left pleural effusion (Fig. 2). The chest CT showed bilateral pleural effusion and mild pleural thickening without hilar lymph node swelling, and the amount of the left pleural effusion was higher than that in the right side, with small air densities in the effusion (Fig. 3). In order to determine the reason for the rapid change in the effusion in

the left thorax, we performed a cytological examination of the left pleural effusion percutaneously. Both left and right pleural effusions were exudative, however, the cell populations were entirely different. The cell fraction of the right pleural effusion was mononuclear cell (mainly lymphocyte and plasma cell) dominant (Fig. 4a). The left one was polymorphonuclear cell (mainly neutrophil) dominant (Fig. 4b). The concentrations of several markers in the right and left pleural effusion were as follows: pH, 8.0 and 7.5; TP, 6.1, 4.9 (g/dL); LDH, 191, 2297 (IU/L); glucose, 116, 2 (mg/dL); and IgG, 2515, 1491 (mg/dL), respectively. Although the cultures of bacteria and acid-fast bacilli in both the left and right pleural effusions were negative, we diagnosed acute bacterial pleuritis for the left thorax. In addition to administration of antimicrobial agents, pleural lavage was performed for 5 days via a catheter. As a result, the left pleural effusion was controlled and the patient was discharged 27 days after admission. At the time of discharge, his bilateral pleural effusion was the same as that observed on admission. ~~Two years after the discharge, his bilateral pleural effusion had not changed significantly (Fig. 5) and his serum concentration of interleukin-6 (IL-6) was normal.~~

(→move)

In order to determine the etiology of his chronic bilateral pleuritis, we re-evaluated the previously obtained parietal pleural biopsy specimens from the left thorax using an

immunostaining method. The numbers of both IgG4-positive and IgG-positive cells were counted in regions of the highest density and averaged in three the most cellular high-power fields (HPF) [2]. The specimens of the left parietal pleural tissue showed lymphoplasmacytic infiltration with mild fibrosis and no granulomas were seen in Hematoxylin and Eosin (HE) staining (Fig. 6a). Interestingly, immunohistochemical examinations showed infiltration by numerous IgG4-positive plasma cells in the specimens (Fig. 6b). The number of IgG4-positive plasma cells per HPF was 17.6, scored as moderate (10-30/HPF) according to Kamisawa *et al.* [4], and the percentage of IgG4-positive to IgG-positive plasma cells (IgG4+/IgG+) was 85.4%. There was a mixture of kappa-positive and lambda-positive cells in the specimens. Furthermore, the concentrations of IgG and IgG4 in the right pleural effusion were higher than those in the serum (the IgG subtypes in the right pleural effusion were as follows: IgG1, 758 mg/dL; IgG2, 651 mg/dL; IgG3, 69 mg/dL; and IgG4, 590 mg/dL). Therefore, the chronic lymphoplasmacytic pleuritis in this patient was diagnosed as IgG4-related pleural disease.

One year later, he developed colon cancer, and underwent a curative resection in 2009. The FDG-PET before the operation showed an abnormal accumulation of FDG in the colon tumor and an ill-defined nodule of the left lung, which was suspected to be an

inflammatory lesion. However, no other abnormal uptake was observed, even in the pleura. Furthermore, the thoracho-abdominal CT showed no remarkable abnormality except for bilateral pleural effusion and colon cancer.

Two years after the discharge, the patient treated with diuretics had no respiratory symptoms and his bilateral pleural effusion had not changed significantly (Fig. 5). His serum concentrations of the IgG subclasses and interleukin-6 (IL-6) in 2010 were as follows: IgG1 1280 mg/dL; IgG2 1000 mg/dL; IgG3 136 mg/dL; and IgG4 754 mg/dL (IgG4/IgG 34.1%), and 1.76 pg/ml (<2.41).

DISCUSSION

We herein described that an elderly male with bilateral chronic lymphoplasmacytic pleuritis developed acute left bacterial pleuritis and finally was identified as having IgG4-related disease 4 years after the appearance of the bilateral pleural effusion. A re-evaluation of the previously obtained biopsy specimens using an immunostaining method revealed numerous IgG4-positive plasma cells in the parietal pleura. Because IgG4-related disease was seldom reported in 2004, we did not measure the serum IgG4 concentration at that time, and thus overlooked the diagnosis of bilateral lymphoplasmacytic pleuritis with IgG4-related pleural disease in this patient.

Rigorous diagnostic criteria for IgG4-related lung and pleural diseases have not been established, however, a high serum concentration of IgG4 and marked IgG4-positive plasma cell infiltration in the biopsy specimens are accepted to be the characteristic features of this disease [1, 2]. The lung and pleural involvement of AIP and Mikulicz's disease were thought to meet the criteria for IgG4-related lung and pleural diseases. Mikulicz's disease is a IgG4-related systemic disease which is identified by an enlargement of the lachrymal and salivary glands, which differs substantially from Sjögren's syndrome [5]. Fujinaga *et al.* reported that the lung lesions were detected in 25 (54%) out of 46 patients with AIP who had undergone thin-slice chest CT scanning [6]. Various extrapancreatic lesions had been reported in AIP and a new clinicopathological entity of IgG4-related autoimmune disease was submitted [4]. Meanwhile, Masaki *et al.* reported that 6 (9.4%) of 64 patients with Mikulicz's disease showed interstitial lung disease and 11 (17.2%) of 64 patients had AIP [7]. They proposed a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome (IgG4+MOLPS), a syndrome characterized by hyper-IgG4 gammaglobulinemia (>135mg/dL) and IgG4-positive plasma cell infiltration in the tissues (IgG4+/IgG+ >50%) [7]. However, there are important limitations of these reports because a large segment of the lung lesions were diagnosed by radiological findings rather than the

pathological findings of the lungs [4, 6, 7]. On the other hand, Zen *et al.* reported 21 patients with IgG4-related lung and pleural disease diagnosed on the basis of the histopathological findings of the lung and pleura [1]. These patients had characteristic HE findings such as diffuse lymphoplasmacytic infiltration, irregular fibrosis, and occasional eosinophil infiltration. The immunostaining showed diffuse IgG4-positive plasma cell infiltration and a ratio of IgG4+/IgG+ greater than 30%. In addition, 9 (43%) out of the 21 patients had IgG4-related disease in other organs, such as the pancreas and submandibular glands [1].

Miyake *et al.* reported a male patient with left pleural effusion and swelling of the submandibular glands diagnosed with Mikulicz's disease [5]. He had a high concentration of serum IgG4 and his biopsy specimens of the submandibular gland showed abundant IgG4-bearing mononuclear cell infiltrations. Although he had not received a lung or pleural biopsy, pleurocentesis was performed on the left thorax, and numerous mononuclear cells (lymphocytes and plasma cells) were present in his plural effusion. Additionally, his IgG4 concentration in the pleural effusion was higher than that in the serum [5]. Similarly, the present patient showed a high serum IgG4 concentration, and his effusion of non-bacterial pleuritis was mononuclear cell (mainly lymphocyte and plasma cell) dominant, and the IgG4 concentration in the effusion was

higher than that in the serum. Furthermore, the biopsy specimens of the left parietal pleura showed numerous IgG4-positive plasma cell infiltrations, in agreement with the criteria for IgG4-related lung and pleural diseases proposed by Zen *et al.*[1] and IgG4+MOLPS [5]. Although his serum concentrations of IgG and IgG4 were high, the electrophoretogram of his blood did not show a monoclonal band. His serum autoantibodies were all negative and the serum concentrations of ACE, ANCA, and IL-6 were normal. Because the other differential diagnoses such as multiple myeloma, collagen vascular disease, sarcoidosis [8], Wegener's granulomatosis, Castleman disease [7, 9], and other malignant diseases were not in agreement with the chronic bilateral pleuritis of the present patient pathologically, we considered the final diagnosis of the patient to be chronic bilateral IgG4-related pleuritis. IgG4-related lesions and lymphomatoid granulomatosis grade 1 (LYG-G1) lesions have been reported to be morphologically indistinguishable from one another in the lung [1, 10]. We also think that the lack of any atypical cells and the presence of IgG4-positive plasma cells may therefore be more indicative of IgG4-related disease over LYG-G1 [10].

To the best of our knowledge, there have been only three other published cases with IgG4-related lung and pleural diseases, diagnosed on the basis of pathological findings of the lung and pleura or pleural effusion, revealed pleural effusion

radiologically [2, 5, 10]. The patient with Mikulicz's disease was treated with 30mg/day predonisolone (PSL) for 14 days, followed by a tapering of the PSL dosage. As a result, the pleural effusion showed a drastic reduction [5].One patient with right pleural effusion was successfully treated with diuretics after the thoracoscopic biopsy [10]. Although the present patient did not receive oral corticosteroid therapy after the diagnosis, his bilateral pleural effusions did not increase and IgG4-related diseases in other organs ~~was~~ were not found by FDG-PET and CT. It was reported that FDG-PET was a sensitive tool for detecting lesions related to IgG4-related disease, and that the levels of FDG uptake revealed the activity of the lesions [11]. However, there have been no reports of patients with IgG4-related pleural disease who were examined by FDG-PET. Because no abnormal accumulation of FDG in the pleura or pleural effusion was observed in the present case, it seems that the activity of IgG4-related pleural disease is relatively low. Furthermore, IgG4-related pleural disease might thus have a relatively favorable prognosis.

~~In conclusion, this is the first report of a patient presenting with chronic bilateral IgG4-related pleuritis who developed acute left bacterial pleuritis~~. In conclusion, there have been some reports of IgG4-related diseases, however, this case is rare due to the fact that this patient was diagnosed to have IgG4-related localized pleural disease, based

on the findings of a pleural biopsy while, in addition, the patient was followed for a substantial length of time and also demonstrated a relatively favorable prognosis.

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FIGURE LEGENDS

Figure 1. A chest X-ray on admission showed bilateral pleural effusion as described without significant infiltration.

Figure 2. A chest X-ray at 7 days after admission revealed a rapid increase in the left pleural effusion.

Figure 3. A chest CT at 7 days after admission showed bilateral pleural effusion and mild pleural thickening. The left pleural effusion was more extensive with small air densities (arrows).

Figure 4. Cytology of the right pleural effusion showed lymphoplasmacytic infiltration (a) and left pleural effusion revealed marked neutrophil infiltration (b). (Giemsa stain x100)

Figure 5. A chest X-ray in 2010 of recent data showing that there was not significant increase in the bilateral pleural effusion.

Figure 6. The left parietal pleural biopsy specimens showed lymphoplasmacytic infiltration with mild fibrosis in Hematoxylin and Eosin (HE) staining (a). An immunohistochemical examination of the specimen revealed dense infiltration of IgG4-positive plasma cells (b). (x 400)

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